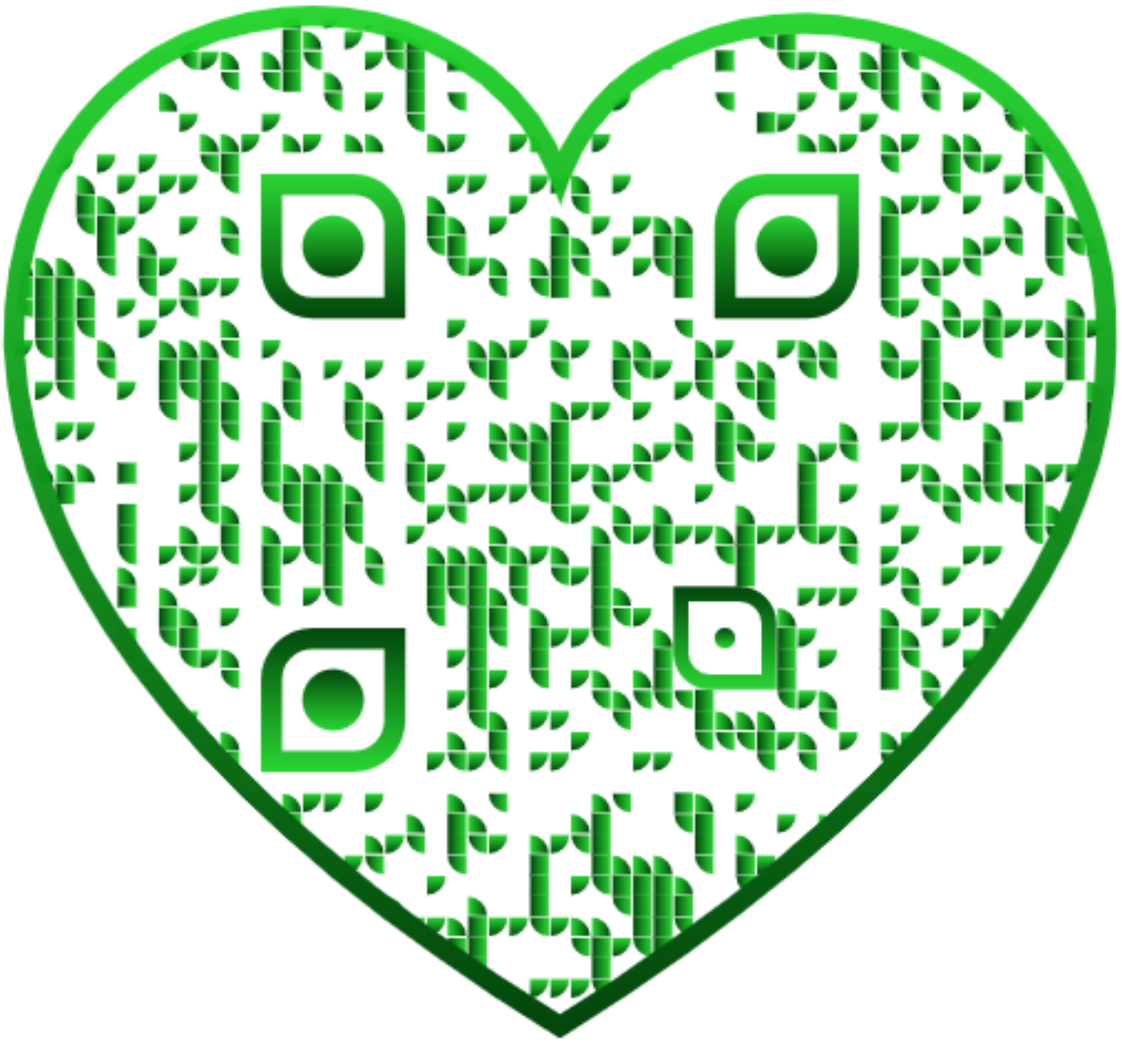
Pharmacovigilance (PV)

Sisay E.



Pharmacovigilance (PV)

- **Etymological origin (roots) for PV**
  - *Pharmaco*= Drug/Medicines
  - *Vigilare* = 'To watch', 'alert watchfulness'
- **WHO Definition of PV**
  - **Science** and **activities** relating to the **detection, evaluation, understanding and prevention** of adverse drug reactions (ADRs) or any other drug-related problems

PV…

- PV is the process of evaluating as well as improving the safety of drugs
- PV can be called as the practice of using scientific methods for tracking, recording, and analyzing the effects of various pharmaceutical products
- It can be named as **“Drug safety”**

Historical developments of PV

- Today's PV concept came into picture succeeding historical incidents that occurred in many parts of the world

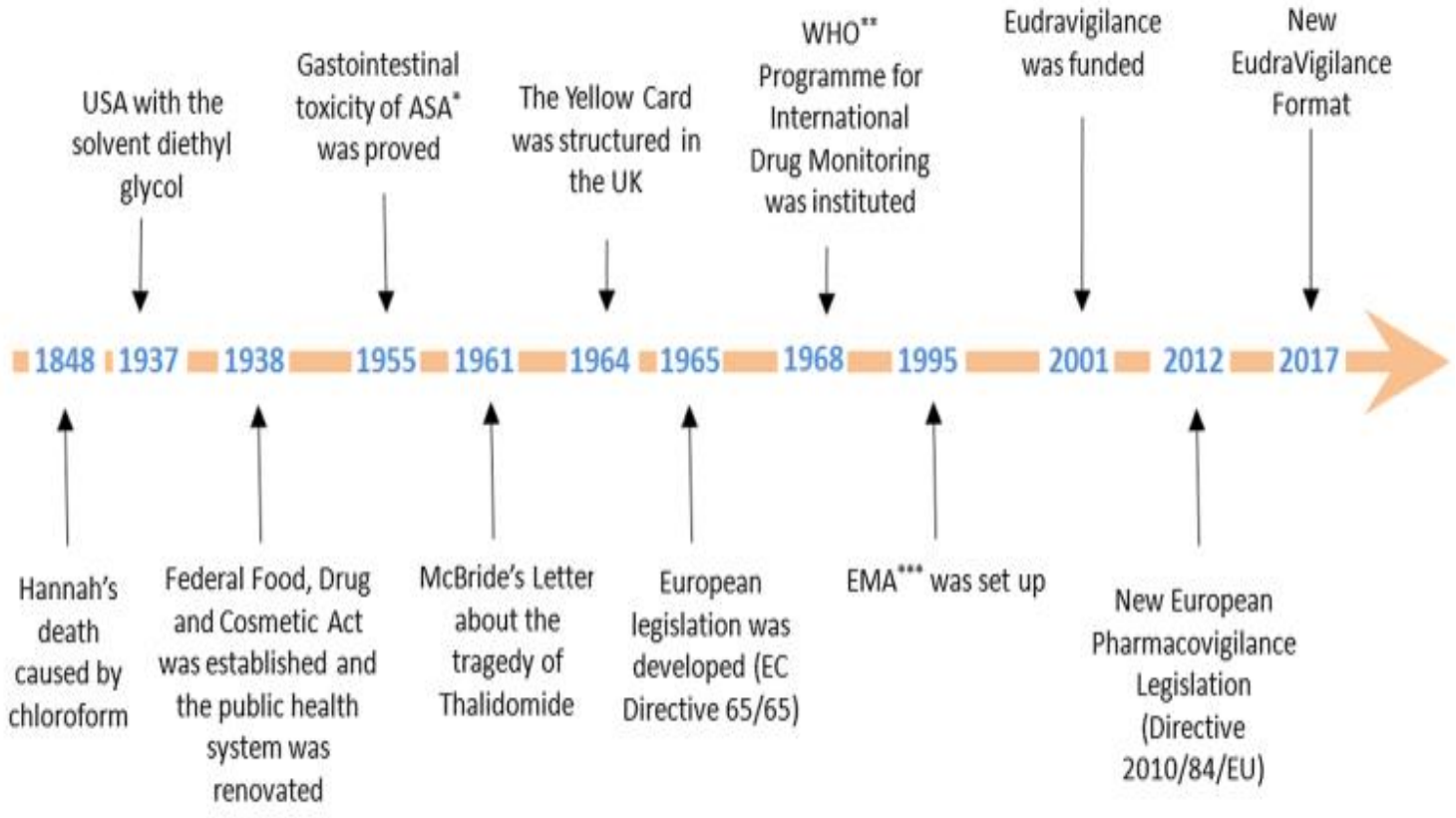


Figure 1 : Timeline of the historical evolution of PV

Historical developments of PV…

- **Thalidomide tragedy**
  - The greatest of all drug disasters was the of 1961-62
  - Thalidomide had been introduced, and welcomed, as a safe and effective hypnotic and anti-emetic
  - It rapidly became popular for the treatment of nausea and vomiting in early pregnancy.
  - Tragically, the drug proved to be a potent human teratogen that caused major birth defects in an estimated 10, 000 children in the countries in which it was widely used in pregnant women
- In 1961, a big change of European PV happened following the tragedy of Thalidomide.

Historical developments of PV…

Figure 2: Picture showing victims of thalidomide tragedy

What has been changed because of the tragedy?

- The thalidomide tragedy taught the world many lessons.
- Some of the main lessons learned includes:
  - The need for **adequate testing** of medicines prior to marketing
  - The need for **government regulation** of medicines
  - The need for **reporting systems** to identify the adverse effects of medicines
  - The potential safety implications of **unproven marketing** claims
  - Most medicines cross the placenta and this results in fetal exposure
  - Avoidance of unnecessary use of medicines in pregnancy
  - Some risks can be successfully minimized.

What has been changed because of the tragedy…

- Direct results of thalidomide incident:
  - **WHO (1968):** Programme for International Drug Monitoring (PIDM)
  - **USA (1962):** Amendment on FDC Act
  - **UK (1964)** : Yellow card scheme
  - **Europe:**
    - European legislation (1965): EC Directive 65/65
    - EudraVigilance (2001)

Scope of Pharmacovigilance

- PV Primarily related to ADRs
- In recent times, it expanded and has grown to include other medication safety issues

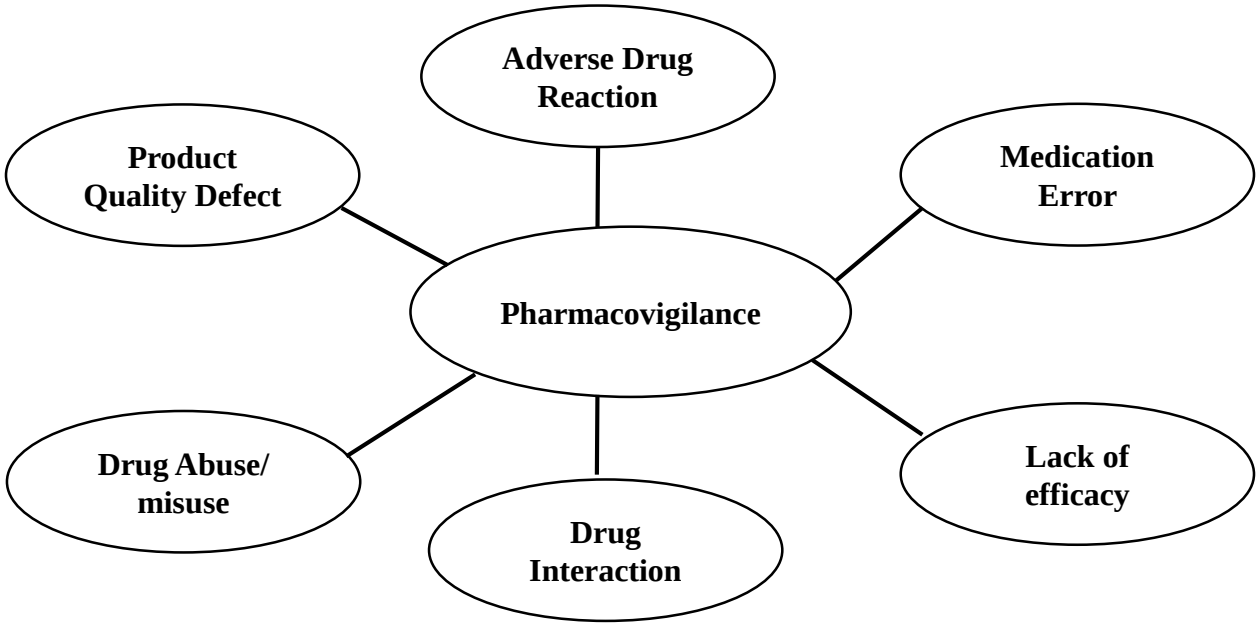


Figure 3: Scope of PV

Products under PV consideration

- PV go beyond conventional medicines

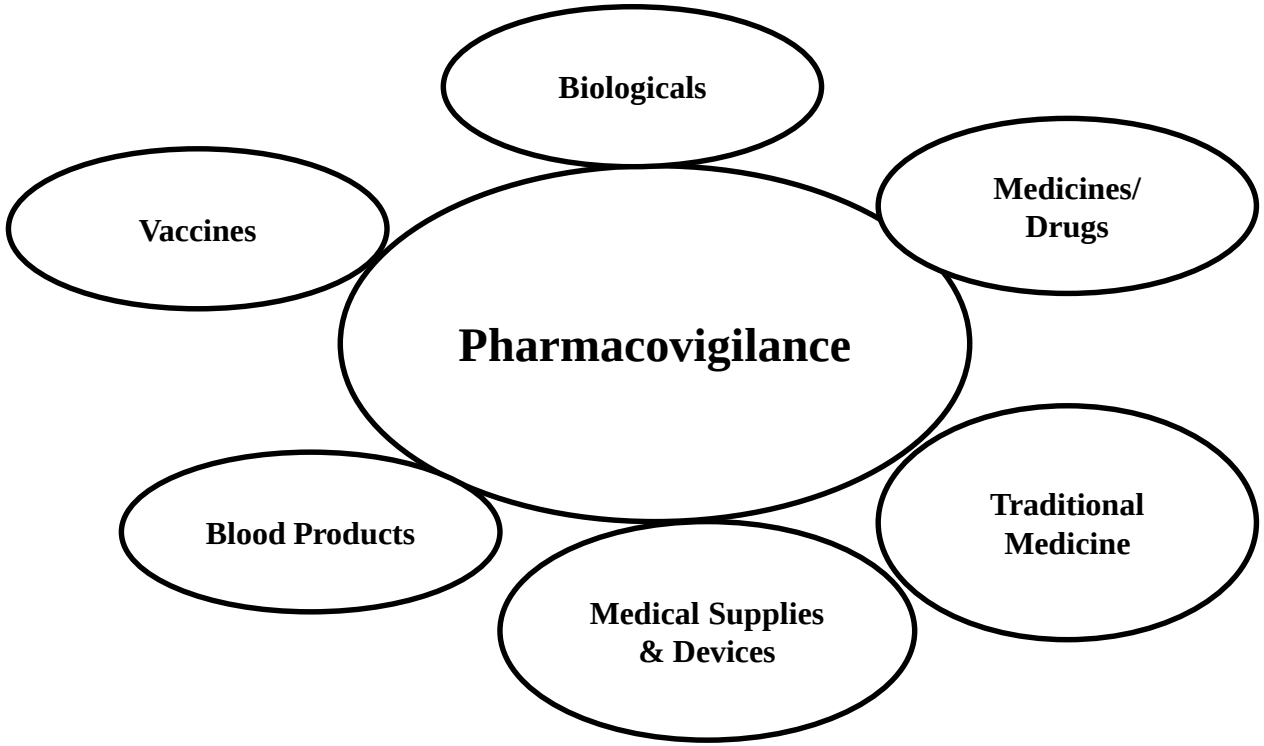


Figure 4: Products covered by PV

Major Aims of Pharmacovigilance

- Early detection of unknown safety problems
- Detection of increases in frequency
- Identification of risk factors
- Quantifying risks
- Preventing patients from being affected unnecessarily

Why Pharmacovigilance?

- **Pre-marketing safety data**
  - Tests in animals are insufficiently predictive of human safety
  - Clinical Trials safety information is incomplete
    - Few patients -- rare events likely to be missed
    - Not necessarily ‘real world’
  - Information about rare but serious adverse reactions, chronic toxicity, use in special groups or drug interactions is often not available.

Why PV…?

- **Post-marketing issues:**
    - Unexpected adverse reactions
    - Interactions
    - Dependence
    - Long-term efficacy
    - Resistance
    - Risk factors
    - Quality (counterfeit)
    - Cost assessment
  - ADRs is becoming the largest cause of mortality

Why PV….?

- Percentage of hospital admissions due to drug related events in some countries is about or more than 10%
- Economic impact
  - Drug-related morbidity and mortality expenses exceeded
- Promoting rational use of medicines and adherence
- Ensuring public confidence
- Ethics:
  - To know of something that is harmful to another person who does not know, and not telling, is unethical

Adverse drug event versus Adverse drug reaction

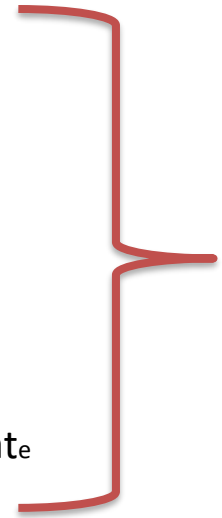
- **Adverse drug event (ADE)**
  - "Any untoward medical occurrence that may be present during treatment with a medicine but does not necessarily have a causal relationship with this treatment,
    - An adverse outcome that occurs while the patient is taking the medicine but is not, or not necessarily, attributable to it
- **Adverse Drug Reaction (ADR)**
  - "A response to a medicine which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

Stakeholders in PV

- **A range of stakeholders are involved in PV activities**:
  - Patients and consumers
  - Healthcare professionals
  - Health facilities
  - Market Authorization Holders (MAH)
  - Public health programmes
  - Regulatory Authority-EFDA
  - Academia and research institutions
  - Professional Associations
  - WHO Collaborating Center for International Drug Monitoring
  - Community leaders
  - Media etc…

Activities to promote medicines safety

- Activities to promote medicines safety entails
  - Monitoring medicine use in order to;
    - Detect potential medicine-related problems
    - Further assesses and understand
    - Develop prevention strategies
- The core activities that will work in a well-established system
  - Monitor
  - Detect
  - Assess
  - Understand
  - Communicate



Preventing patients from medicine-related injuries

Outcome from PV activities

- Information from spontaneously reported ADEs, published literature, clinical and epidemiological studies is used as the primary basis for decision making including;
    - Restricted use of the product in certain patient populations
    - Dosage adjustments
    - Added warnings
    - Withdrawal of the product

Adverse drug events to be reported

- Adverse Drug Events (medicine-related injuries), with at least a reasonable possibility to be caused by:
  - Direct pharmacological mechanism of a medicine
  - An individual's particular vulnerability
  - Drug interactions
  - Unexpected therapeutic ineffectiveness
  - Medication errors
  - Product quality defects
  - Malfunction or deterioration in the characteristics or performance of in-Vitro Diagnostic device.
  - False positive or false negative test result falling outside the declared performance of the test

Alphabetical categorization of ADRs

- **Type A (Augmented)**
  - Related to the principal action of the medicine
  - Can occur in anyone
  - Dose related
  - Pharmacodynamic effects
  - Common
  - Skilled management reduce their incidence

Alphabetical categorization of ADRs…

- **Type B (Bizarre)**
  - Not related to the principal action of the medicine
  - Will occur in some people
  - Not part of the normal pharmacology of the medicine
  - Not dose related
  - Unpredictable
  - Include idiosyncrasy and drug allergy
  - Account for most drug fatalities

Alphabetical categorization of ADRs…

- **Type C (continues)**
  - Reaction due to long-term use
- **Type D (delayed)**
  - Effects like teratogenesis, carcinogenesis
- **Type E (ending of use)**
  - Abrupt discontinuation
  - e.g. rebound adrenocortical insufficiency
- **Type F (failure of therapy)**
  - AMR

Major factors predisposing to adverse effects

- Extremes of age
- Inter current illness:
  - If the patient also suffers from another disease, such as kidney, liver or heart Disease
- Drug Interactions
  - Interactions may occur between drugs which compete for **the same receptor or act on the same physiological system.**

Major factors predisposing to adverse effects…

- Incompatibilities between medicines and IV fluids;
  - pH changes, precipitation, chemical reaction
    - **Example**: Benzyl penicillin and Ampicillin lose potency after 6-8 hours if added to dextrose solutions, due to the acidity of these solutions
- Traditional medicines
- Effect of food on drug absorption

Stakeholders Roles and responsibilities in PV

- **Patients and Consumers**
  - Should report to any healthcare professional
    - Prescriber, dispenser or administered the drug
  - Health professionals report to EFDA
- **Healthcare professionals**
  - Being vigilant and detecting adverse drug events
  - Assessing the patient
  - Reporting

Healthcare professionals…

1. Being vigilant and detecting adverse drug events

- Any unexpected sign, symptom or complaint voiced by patients taking medicines
- Distinguish between the natural progression of a disease and an adverse effect by a medicine
- Monitor for medication errors whilst prescribing, transcribing dispensing and administering medicines to patients.
- Make physical inspections of the medicinal products (Color changes, separating components, powdering, crumbling, caking, molding, change of odor, incomplete pack, suspected contamination, poor packaging/poor labeling)

Healthcare professionals…

2. Assessing the patient

– When a medicine-related problem is suspected, the clinician should carry out a thorough **physical examination** with appropriate laboratory tests and consider:

- The patient's medical history, including **allergy**
- The existence **of any potential risk factors**, such as hepatic or kidney insufficiency
- The existence of **risk groups such as pediatric**, elderly, pregnant and lactating patient

Healthcare professionals…

- The clinician should treat the patient and consider to:
  - Adjust the **dose** or
  - **Replace** the medicine or
  - Withdraw the medicine
- **The patient should be informed about** the suspicion of the ADR and what actions are planned.
- **Careful documentation** of the ADR in the patient's medical records should take place

Healthcare professionals…

- **3. Reporting**
  - Suspected ADRs, detected medication errors or product quality defects should be reported to the PV center at EFDA.
  - Adverse Event Reporting tools in Ethiopia
    - **Yellow form: Prepaid report available at the facility**
    - **Web -based (E-reporting)**
    - **Mobile application: Medsafety**
    - **Toll free line: 8482**
    - **Telephone: 01115523142 (direct) or 0115524122 (via operator)**
  - All ADEs ranging from **minor reactions** to **disability** or **death** should be reported.

Healthcare professionals…

- Emphasize should be given to new medicines, serious ADRs, unexpected reactions and drug interactions.
- The reporter does not need to prove that there is a **causal association** between drug and adverse reaction.
- Reports relating to medication errors should specify information on the **product**, **sequence** of events up to the time of error, **work** circumstances during error, and type of error.
- **Report as soon as possible**

Drug and Therapeutic Committee (DTC) at the health facility

- DTC should do the following activities
- **1. Processes to detect adverse drug events**
  - Implement programs to **track ADRs, medication errors and product quality defects**
  - **Review of ADEs**, medication errors or near misses, patient chart review, or physical inspection of products.
  - **A focal person** should be assigned to coordinate all ADE monitoring activities in the facility
    - Serve as a link between the facility activities and the national PV centre.

Drug and Therapeutic Committee at the health facility…

- **2. Assessing adverse drug events**
  - Obtain a **detailed history of the patient** including current health status, current pharmaceutical therapy, and past medical history.
  - Use an ADR reporting form to organize reporting.
    - Identify and document the clinical reaction.
    - Check the product information: known or unknown??
      - If any plausible mechanism of the medicine.

Drug and Therapeutic Committee at the health facility…

- Establish the cause
    - Use the Naranjo algorithm (or other system) for assessing the reaction and establishing the cause
    - The scores for all items are added to give a probability
  - Evaluate the quality of the product from the manufacturer to rule out any ADE occurring from a poor-quality product
    - Pharmaceutical counterfeiting
    - Overt contamination of the product

DTC at the health facility…

- **3. Action in health facility**
  - DTC initiate discussions about analyzed medicine-related problems on a regular schedule
  - Design interventions, methods, procedures that will prevent similar errors to re-occur in the future at the facility.
  - Definitive decision can be made upon the facts as presented
    - Educate the health providers concerning ADEs in
    - In-service education
    - Face-to-face education with providers
    - Medicine information bulletins
    - Change facility specific medicine list if necessary, to obtain a medicine of proven safety.
    - Modify patient monitoring procedures.
  - Medication errors should be reported to EFDA

Marketing Authorization Holders (MAH)

- Pharmaceutical manufacturers
- Importers
- Wholesalers
- Distributors
  - Has the prime responsibility to monitor safety of their marketed products

Marketing Authorization Holders

1. Monitoring for adverse drug events

- **MAH:**
  - Need to have PV system in place
  - Accept responsibility and liability for its registered medicinal products in Ethiopia
  - Should ensure that information on ADEs are collected and collated and communicated to the EFDA
  - Should monitor international scientific literature for new reports at least monthly

Marketing Authorization Holders…

- **Reporting timelines**
  - For Serious ADRs, unexpected and expected
    - 15 calendar days of initial receipt of the information by the MAH.
  - Non-serious ADRs
    - within 90 days
- A serious adverse event or reaction:
  - Any untoward medical occurrence that at any dose:
    - Results in death
    - Life-threatening
    - Requires inpatient hospitalization or prolongation of existing hospitalization
    - Results in persistent or significant disability/incapacity
    - Congenital anomaly/birth defect
    - Other medically important event or reaction

Marketing Authorization Holders…

- **Reports from post-registration studies**
  - All suspected serious ADRs in post-registration studies should be reported
- **Periodic safety update report (PSUR)**
  - For new medicines, PSUR should be submitted to EFDA
    - Every 6 months the first two years after market approval
    - Annually for three years
    - If no ADRs have been received by the MAH, they are obliged to submit a **"Null" report**

Marketing Authorization Holders…

- **Reporting of significant action taken by foreign agency**
  - Any significant safety issue or action taken by foreign agency
    - within 3 calendar days of first knowledge
      - **Example**: an in vitro, animal, epidemiological, or clinical study with significant human risk
- Information on withdrawal of the registration status in any country
  - Must be noted to EFDA within 24 hours of the first knowledge by the MAH

Marketing Authorization Holders…

- Notification of change in product safety profile:
  - Change the label of the product
  - Change in indications, recommended dosage, contraindications, special precautions, warnings or the ADRs section
  - Withdrawn from the market

Marketing Authorization Holders…

2. Risk management plan (RMP)

- Risk management involves:
  - Characterization of what is known or not known about the risk
  - Planning PV activities to gain more knowledge and new information about the risk
  - Planning and implementing risk minimization strategies and evaluate the effectiveness of these activities.

Marketing Authorization Holders…

- **RMP:**
  - Should be prepared and submitted by the MAH at the time of new drug application
  - Significant change in marketing authorization (new dosage form, route of administration, indication)
  - Significant new safety concern
  - Request by EFDA
- Regulatory authority will review the RMP and thereafter approve or request amendments to the document

Public Health Programmes (PHPs)

- Goal of PHP: To promote health and reduce disease, premature death and disease-related discomfort and disability in the population.
- **1. Monitoring medicines**
  - Decide priorities regarding monitoring of medicines
  - How the medicines should be monitored
  - Duration of the monitoring,
  - When adverse reactions should be reviewed
  - The time frames for reporting and actions if a safety concern emerges.
- **Reporting adverse drug events**
  - Suspected ADRs, product quality defects and medication errors

Regulatory Authority-EFDA

1. Report entry

- Enter incoming reports into the national PV database
- Each report is classified as an ADR, medication error or a product quality problem.
- Report will be carefully reviewed (the quality of report and completeness of the medical information)
- Provides feedback to the reporter and might request information in case of missing pertinent data.
- Causality assessment is performed
- Report is classified according to the WHOUMC causality criteria.
- Outcome of the report will be communicated to the appropriate stakeholder.

EFDA…

2. Monitor to detect signals

- **Signal:**
  - "Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously." An additional note says
  - New potentially causal drug and event associations, or a new aspect of a known association, i.e
    - Previously unknown ADRs
    - Increases in frequency of known ADRs
    - Risk groups, risk factors and possible mechanisms underlying ADRs.

EFDA…

- A signal can initially be detected
  - Single incoming report
  - Literature (WHO Signal document and WHO Pharmaceutical Newsletter
  - Post marketing surveillance (PMS)

EFDA…

3. Assessing potential signals

- Each detected potential signal further evaluated
  - Databases, published literature and information from the MAH are reviewed for similar cases
  - National Drug Advisory Committee is provided summary information for evaluation
  - The committee recommends action needs to be done
    - Signal, no signal, or if further monitoring is needed
- Signals related to medication errors
  - evaluated to decide on preventative actions , assessment
- Product quality problems
  - The authority conduct for testing

EFDA…

- **4. Preventative action**
- When a signal has been confirmed, action is taken
  - Letters to healthcare providers about the safety concern
    - Warning
    - Recommend a continued vigilance in prescribing and dispensing the medicine.
  - Package insert revisions
    - Changing the official labeling
    - Changing the package insert to reflect the new safety concern
  - Modifying inadequate designs of product labeling, packaging, product formulation, medical device, or product/technical information.
  - Medicine recalls

National Drug PV Advisory Committee

- Recommends what action to be taken by the authority
  - Assessing potential signals
  - Action recommended
  - Communicates findings and recommendations to the EFDA as early as possible.

Academia, research institutions and Professional association

- **Academia, research institutions**
  - Provide training about safe and rational use of medicines, the nature of ADRs, the specifics of medication errors, and the importance to be vigilant of product quality problems.
- **Professional association**
  - Build the capacity of their members trainings on PV and continuing education programs

WHO Collaborating Centre for International Drug Monitoring

Uppsala Monitoring Centre

- Pooling existing data on ADRs
  - WHO's Programme for International Drug Monitoring was started in 1968
  - The WHO Collaborating Centre analyses the reports in the database to:
    - Identify early warning signals of serious adverse reactions to medicines
    - Evaluate the hazard

WHO Collaborating Centre…

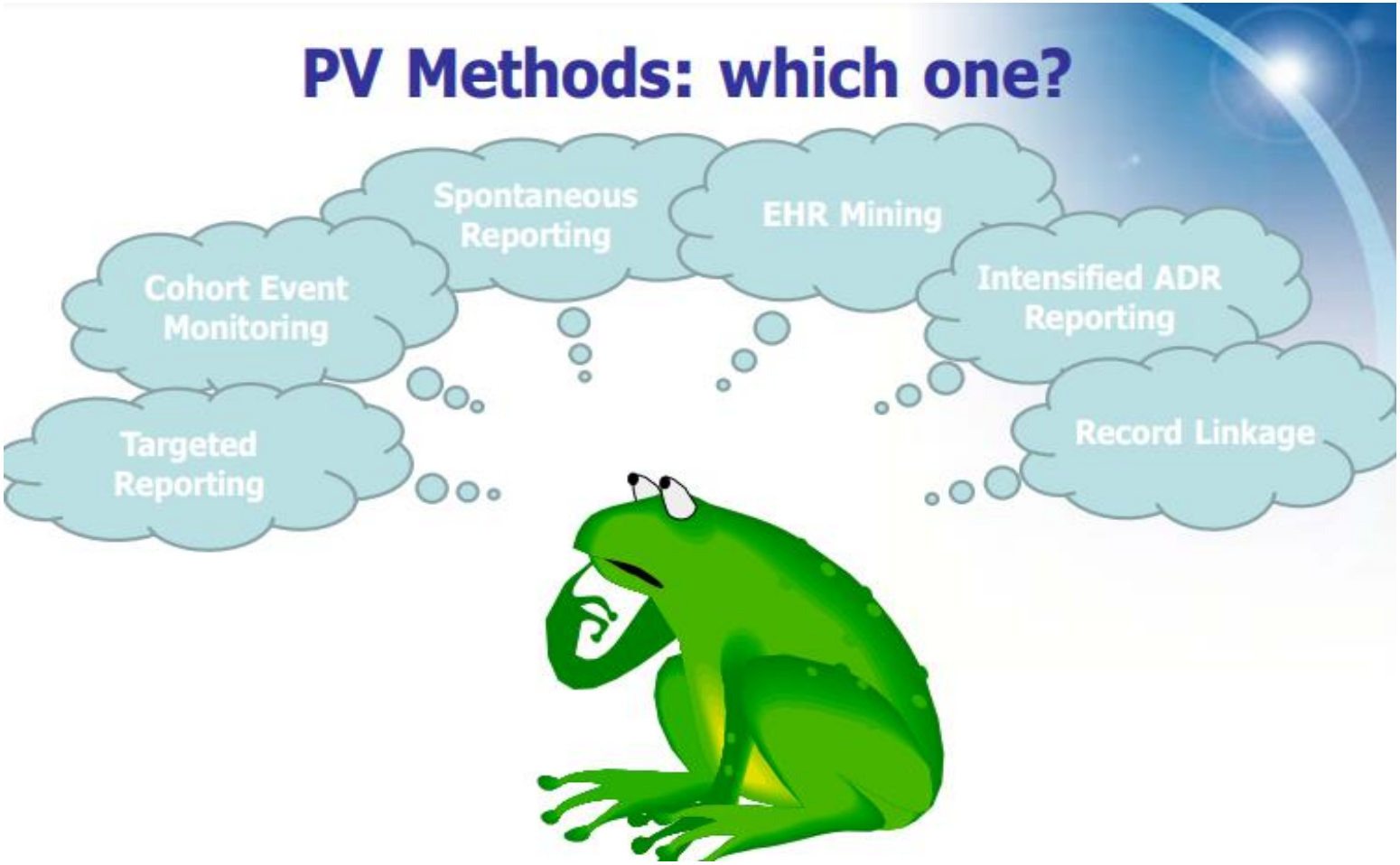
- Undertake research into the mechanisms of action to aid the development of safer and more effective medicines.
- WHO plays an important role in:
  - Provision of expert advice on all matters relating to the safety of medicines
  - Facilitate consistent policies and action among member countries

Other partners

- Media, advocacy groups, and lawyers
  - Directly or indirectly facilitate the development of new and robust drug policies and decisions,
  - Highlight deficiencies and weaknesses in existing drug safety policies

Pharmacovigilance Methods

Pharmacovigilance Methods



Pharmacovigilance Methods

- Several methods can be used to collect safety information in PV.
- Common PV methods includes the following
  - 1. Passive Surveillance
  - 2. Active Surveillance
  - 3. Stimulated Reporting
  - 4. Comparative Observational Studies
  - 5. Targeted Clinical Investigations
  - 6. Descriptive Studies

Passive Surveillances

- Involves the usage of spontaneous adverse event reports voluntarily sent by HCPs or patients to the marketing authorization holder or regulatory authority.
- Reporting is entirely dependent on the initiative and motivation of the potential reporters without no active measures
- The most common PV method
- Commonly referred to as “spontaneous” or “voluntary” reporting.
- In some countries, this form of reporting is mandatory

Passive Surveillances…

- Among passive surveillance system, the following are the common one
  - **Spontaneous reports**
  - **Case series**

Spontaneous reporting system

- An unsolicited communication by HCPs or consumer to a company, regulatory authority or other organization (e.g. WHO, regional Centre, poison control centre)
- Describes one or more adverse reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme

Spontaneous reporting system…

Spontaneous Reporting

Objective: a functional ADR reporting system to monitor the safety of all medicines

- **Voluntary submission of ICSRs by health professionals, pharmaceutical manufacturers (and patients) to the national pharmacovigilance centre**
- **Requires two initial steps:**

  A patient or health professional

  1. **suspects that an undesirable medical event may have been caused by exposure to a medicine**
  2. **reports the suspicion to the national pharmacovigilance centre**

Spontaneous reporting system…

Spontaneous Reporting

Pros	Cons
Covers the whole population	Inherent under-reporting
Includes all medicines	Captures only suspected ADRs
Continual monitoring throughout life-cycle of a medicine	Reporting bias e.g. Seriousness, severity New medicine Advertising of product Publicity of specific ADR
Detects signals of new, rare or serious ADRs	Denominator unknown
Most commonly used method	Difficult to detect – delayed ADRs &
Easiest method to establish	– ADRs with high background incidence
Relatively inexpensive	
Least labour intensive	

Case series

- Series of case reports can provide evidence of association between a drug and an adverse event.
- More useful for generating hypotheses than for verifying an association between drug exposure and outcome.
- Certain distinct adverse events known to be associated more frequently with drug therapy
  - **Example:** Anaphylaxis, aplastic anemia, toxic epidermal necrolysis and Stevens - Johnson syndrome.
    - When events such as these are spontaneously reported, PV centers should place more emphasis on these reports for detailed and rapid follow-up.

Intensified (Stimulated) reporting

- **Objective:** To enhance ADR reporting of specific medicines in early post -marketing phase
  - Mostly for new products for early post authorization
- Extension of spontaneous reporting programme
  - **Example:** Black Triangle (UK)

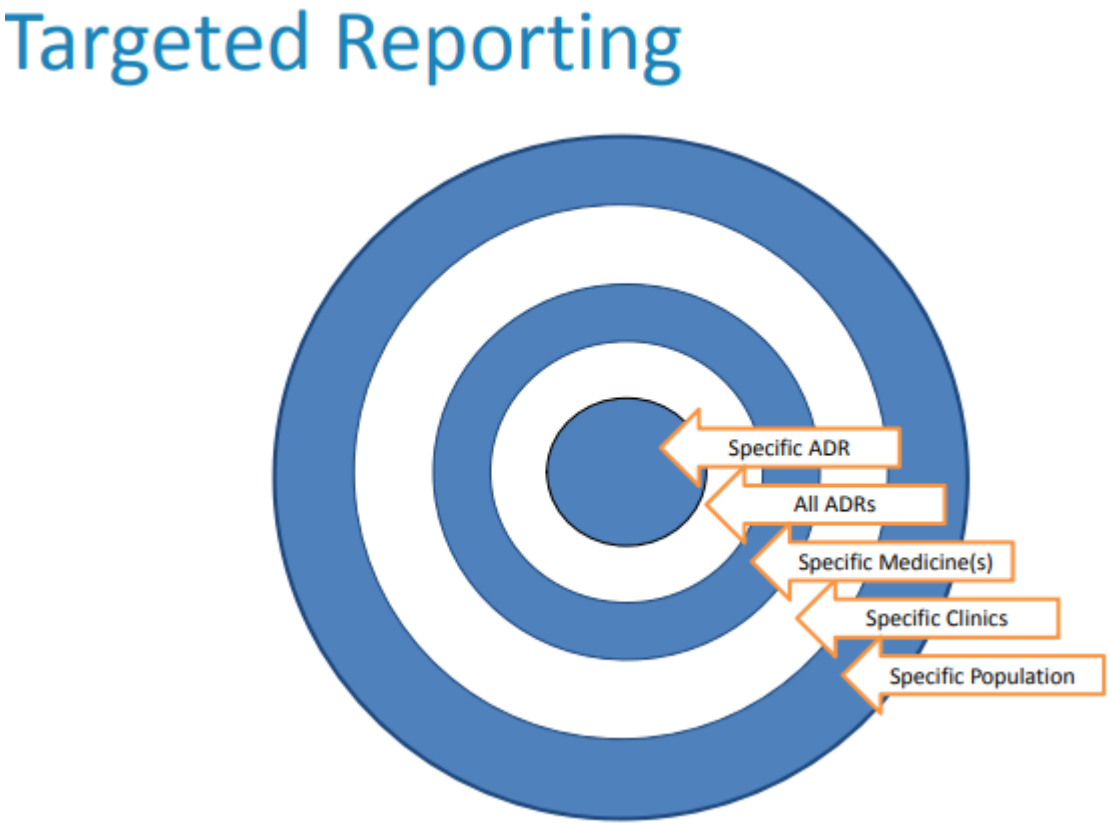
Targeted Spontaneous Reporting (TSR)

- **Objective:**
  - To learn more about the ADR profile of a specific medicines in the population
  - To estimate the incidence of a known ADR to a specific Population

TSR…

- Intensified ADR Reporting within a defined cohort
  - TSR Uganda: Specific population: Patient with HIV infection
    - **Specific clinics**: Regional Pharmacovigilance Centres of Masaka and Mbale
    - **Specific population**: Patient with HIV infection
    - **Specific medicines**: Tenofovir
    - **Specific ADRs**: Renal toxicity

Targeted spontaneous reporting…



Targeted spontaneous reporting…

Drug Saf (2015) 38:395–408
DOI 10.1007/s40264-015-0277-9

ORIGINAL RESEARCH ARTICLE

Targeted Spontaneous Reporting of Suspected Renal Toxicity in Patients Undergoing Highly Active Anti-Retroviral Therapy in Two Public Health Facilities in Uganda

Helen Ndagije · Victoria Nambasa · Elizabeth Namagala · Huldah Nassali · Dan Kajungu · Gordon Sematiko · Sten Olsson · Shanthi Pal

Targeted spontaneous reporting…

Pros with TSR

- Can utilise existing ADR reporting infrastructure
- Targets specific medicines of interest
- Possible to implement monitoring programme that targets specific issue of concern (ADR, medicine, patient group)
- Captures useful information (less 'background noise')
- Denominator known

Targeted spontaneous reporting…

Cons with TSR

- Under-reporting remains a problem
- Captures only suspected ADRs or known toxicities
- May limit reporting only to specific ADRs
- Relies on diagnostic capability of reporter

Cohort Event Monitoring (CEM)

- **CEM** is a prospective, observational, cohort study of AEs associated with one or more medicines.
- It is a modification of drug event monitoring
- The surveillance study is planned prior to beginning the treatment with the medication.
- A group of people are exposed to a drug for a defined period and actively followed up during treatment

Cohort Event Monitoring (CEM)…

- Important to gather more information on the safety profile of a new chemical entity in early post- marketing phase
- Observational cohort study design
- Patients enrolled into cohort and actively followed-up during treatment to record all adverse events (not just suspected ADRs)

Cohort Event Monitoring (CEM)

- Characterize known reactions
- Detect signals of unrecognized reactions
- Identify interactions with other medicines and TCAMs
- Detect inefficacy of medicine
- Assess safety in pregnancy & lactation
- Identify risk factors for ADRs

CEM…

Cohort Event Monitoring

Pros	Cons
Early detection of signals of unsuspected ADRs	More labour intensive than SR or TSR
Denominator information allows incidence rates of ADRs to be calculated	More costly
Near complete profile of AEs/ADRs for medicine of interest	Much data collected most of which represents 'background noise'
Assessment of risk; identification of risk factors; between drug comparisons	New to health professionals and PV Centres
Pregnancy outcomes	Training required
Deaths recorded	LTFU may be substantial and needs to be actively managed

Active Surveillances

- Seeks to ascertain completely the number of adverse events via a continuous preorganized process
- Provides stimulus to health care workers in the form of individual feedback or other incentives
- Aims to monitor certain specific drug-related adverse events and seeks to ascertain the number of adverse drug reactions entirely through a pre-planned process
- Active measures are taken to detect adverse events.

Active Surveillances…

- This surveillance is best done prospectively.
- It sometimes very descriptively referred to as hot pursuit.
- It seeks to completely ascertain the number of adverse events via a continuous pre-organized process
- **Examples of active surveillance systems:**
  - **Sentinel Sites**
  - **Drug Event Monitoring**
  - **Registries**

Sentinel Site

- Involves collection of Adverse events (AEs) data from only part of the total population to learn something about the larger population
- Active surveillance can also be achieved by reviewing medical records or interviewing patients and or physicians in a sample of sentinel sites to ensure complete and accurate data on reported AEs from these sites.
- Used when high-quality data are needed about a particular disease or medicine that cannot be obtained through a passive system
- Deliberately involves only a limited network of carefully selected reporting sites

Sentinel Site…

- Selected reporting units with the following characteristics
  - High probability of seeing cases of the disease in question
  - Good laboratory facilities and experienced well-qualified staff
  - Identify and notify on certain diseases.
- **Drawback:**
  - Selection bias
  - Small number of patients
  - Increased cost

Drug event monitoring

- Patients might be identified from electronic prescription data or automated health insurance claims.
- Follow up questionnaire can then be sent to each prescribing physician or patient at pre-specified interval to obtain outcome information
- **Limitations:**
  - Poor physician and patient response rates and
  - Unfocussed nature of data collection, which can obscure important signals
  - In addition, maintenance of patient confidentiality might be a concern.
- On the other hand, more detailed information on adverse events from a large number of physicians and or patients might be collected.

Registries

- A list of patients presenting with the same characteristics will be studied or followed
- It can be;
  - Disease (disease registry)
  - Specific exposure (drug) registry
  - Pregnancy (pregnancy registry)
- Collect information using standardized questionnaires in prospective fashion
- **Disease registries:**
  - Can help collect data on drug exposure.
  - Can also serve as a base for a case control study

Registries…

- **Exposure/drug registry:**
  - Addresses population exposed to medicinal products of interest to determine if the drug has a special impact on this group of population
- **Pregnancy registry:**
  - Some exposure registries address drug exposures in specific populations such as pregnant women

Comparative Observational Studies

- A number of observational study designs are useful in validating signals from spontaneous reports or case series.
- Major types of these designs includes:
  - Cross-Sectional Study (Survey)
  - Case-Control Study
  - Cohort Study
  - Use of databases

Cohort Studies

- a population-at-risk for the disease (or event) is followed over time for the occurrence of the disease (or event)
- Information on exposure status is known throughout the follow-up and hence incidence rates can be calculated.
- comparison cohorts of interest are selected on the basis of drug use and followed over time
- Multiple adverse events can also be investigated using the same data source in a cohort study

Cross sectional Studies

- Data collected from a population of patients at a single point in time (or interval of time) regardless of exposure or disease status.
- primarily used to gather data for surveys or for ecological analyses
- major drawback: relationship between exposure and outcome cannot be directly addressed.
- Adv:best used to examine the prevalence of a disease at one time point or to examine trends over time, when data for serial time points can be captured.

Case-Control studies

- cases of disease (or events) are identified.
- Controls, or patients without the disease or event of interest, are then selected from the source population
- The controls should be selected : the prevalence of exposure among the controls represents the prevalence of exposure in the source population.
- exposure status of the two groups is then compared using the odds ratio.

Descriptive Studies

- Natural history of disease
- Drug utilization study (DUS)

- primarily used to obtain the background rate of outcome events and/or establish the prevalence of the use of drugs in specified populations.

1. Natural history of disease: focused on the natural history of disease, including the characteristics of diseased patients and the distribution of disease in selected populations, as well as estimating the incidence and prevalence of potential outcomes of interest

1. Drug utilization study: These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, gender, concomitant medication, and other characteristics.

Summary

Comparing the methods

Method	Medicines	Population	Reports
Spontaneous Reporting	All medicines, life-cycle of product	All exposed individuals but denominator unknown	All ADRs
Intensified ADR Reporting	Specific medicines	All exposed individuals but denominator unknown	All ADRs
Targeted Reporting	Specific medicines	Defined cohort	Specific ADRs
			All ADRs
Cohort Event Monitoring	Specific medicines	Defined cohort	All Events
EHR Mining	All medicines	Defined cohort	All Events

End of the course

Thank You!